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Via mail and e-mail <jameson@niehs.nih.gov>

Dr. C. W. Jameson
National Toxicology Program
Report on Carcinogens
79 Alexander Drive
Building 4401, Room 3118
P.O. Box 12233
Research Triangle Park, NC 27709

Re: Report on Carcinogens/Vinyl Chloride

Dear Dr. Jameson:

The National Toxicology Program (NTP) recently invited public comment on an updated list of nominations for the 12th Report on Carcinogens (RoC). 70 Fed. Reg. 60548 (October 18, 2005). One of the listed groups is "vinyl mono-halides as a class," including vinyl chloride. Vinyl chloride is listed in the 11th and previous editions of the RoC as a "known human carcinogen."

The Vinyl Chloride Health Committee (VCHC) of the American Chemistry Council represents the US manufacturers of vinyl chloride.¹ On July 1, 2004, the VCHC provided the enclosed comments in connection with the first list of nominations for the 12th RoC. In that submission, the VCHC specifically requested NTP to revise the entry for vinyl chloride in the 11th RoC, which had not at that time been published. Thereafter, the 11th RoC was published, and it includes the following entry for vinyl chloride:

Carcinogenicity (*current 11th RoC entry for vinyl chloride*)

Vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. The strongest evidence that vinyl chloride causes cancer in humans is based on numerous epidemiological studies and case reports that show its

¹ Members of the VCHC include: The Dow Chemical Company, Formosa Plastics Corporation, U.S.A., Georgia Gulf Corporation, Oxy Vinyls, LP, PPG Industries, Inc., and PolyOne Corporation.



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association with angiosarcoma of the liver, a very rare tumor. Several studies also have reported that exposure to vinyl chloride causes cancer at other tissue sites including the liver (tumors other than angiosarcoma), brain, lung, lymphatic system, and hematopoietic system (organs and tissues involved in production of blood) (IARC 1987).

Since vinyl chloride was listed in the *First Annual Report on Carcinogens*, epidemiological studies have continued to provide strong evidence for an association with liver cancer (predominantly angiosarcoma of the liver) and somewhat weaker evidence for an association with brain cancer. As of 1999, 197 cases of vinyl chloride-associated angiosarcoma of the liver have been reported including 50 in the United States. Additionally, recent studies suggest that lung cancer, lymphoma, and leukemia may not be associated with vinyl chloride exposure (Kielhorn *et al.* 2000).

The new entry in the 11th RoC is a significant improvement over the previous entry, which contained a number of erroneous statements associating vinyl chloride with various cancers. While the entry in the 11th RoC is an improvement over the 10th RoC, further changes are needed in order for the entry in the 12th RoC to provide an accurate statement as to the strength of the evidence for such associations. Set forth below is a redlined version of the 11th RoC entry reflecting the changes that we recommend:

Carcinogenicity (*Requested revisions for the 12th RoC entry for vinyl chloride*)

Vinyl chloride is *known to be a human carcinogen* based on sufficient evidence of carcinogenicity in humans. The strongest evidence that vinyl chloride causes cancer in humans is based on numerous epidemiological studies and case reports that show its association with angiosarcoma of the liver, a very rare tumor. Several studies also have reported that exposure to vinyl chloride causes cancer at other tissue sites including the liver (tumors other than angiosarcoma), brain, lung, lymphatic system, and hematopoietic system (organs and tissues involved in production of blood) (IARC 1987).

Since vinyl chloride was listed in the *First Annual Report on Carcinogens*, epidemiological studies have continued to provide strong evidence for an association with liver cancer

(predominantly angiosarcoma of the liver) . As of 1999, 197 cases of vinyl chloride-associated angiosarcoma of the liver have been reported including 50 in the United States. More recent epidemiological studies, however, including a meta-analysis by the authors of the most recent updates of European and American industry-wide cohorts of workers exposed to vinyl chloride, do not support an association between vinyl chloride exposure and cancers other than those of the liver and soft tissue (Boffetta *et al.* 2003).

In addition to the points made in the enclosed VCHC submission, which is incorporated by reference into these comments, the recommended changes are supported by a paper by the Chief of the Occupational Studies Section of the US National Cancer Institute, which states that epidemiological evidence shows a strong exposure-response relationship for angiosarcoma of the liver, but not for other types of cancer.² A more recent review reaches the same conclusion: "Occupational vinyl chloride exposure has not been conclusively causally linked to any adverse health outcome, with the exception of angiosarcoma of the liver."³ And a still more recent review states: "The aggregate data . . . are reassuring in excluding any excess risk of death from lung, laryngeal, soft tissue sarcoma, brain and lymphoid neoplasms, as well as cirrhosis."⁴

As indicated in the earlier VCHC submission, recently published updates of cancer incidence in European and American industry-wide cohorts of workers exposed to vinyl chloride provide a firm basis for the conclusion that vinyl chloride exposure is not causally associated with brain cancer. The European study was conducted by scientists affiliated with the US National Institute of Occupational Safety and Health (NIOSH) and the International Agency for Research on Cancer (IARC) of the World Health Organization. It found no evidence of an increase in cancers other than angiosarcoma of the liver.⁵ Specifically, with regard to brain cancer, which "was of *a priori* interest on the basis of findings in some prior studies," "[e]vidence for an association of brain cancer with VC [vinyl chloride] exposure in the current study was generally negative."

² Blair A and Kazerouni N. Reactive Chemicals and Cancer. *Cancer Causes and Control* 1997; 8:473-90.

³ McLaughlin JK and Lipworth L. A critical view of the epidemiologic literature on health effects of occupational exposure to vinyl chloride. *J Epidemiol Biostat* 1999; 4:253-75.

⁴ Bosetti, C, LaVecchia C, Lipworth L, McLaughlin, JK. Occupational exposure to vinyl chloride and cancer risk: a review of the epidemiologic literature. *Euro J Cancer Prevention* 2003; 12:427-30.

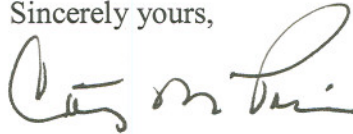
⁵ Ward E, Boffetta P, Andersen A, Colin D, Comba P, Deddens JA, *et al.* Update of the follow-up of mortality and cancer incidence among European workers employed in the vinyl chloride industry. *Epidemiology* 2001; 12:710-18.

An update of the American cohort has also been published.⁶ This study had identified an excess of mortality from brain cancer, but noted "the size of that excess has decreased with time . . . substantially during the most recent follow-up period," and that "no firm conclusion may be made about an association with vinyl chloride."

Finally, the strongest support for the revision suggested above comes from a meta-analysis published by authors of the most recent updates of the European and American cohorts. This group indicates that the only causes of death in the two "multicenter" studies which had standardized mortality ratios (SMRs) greater than 2, and 95% confidence intervals (CIs) that did not span unity, were liver and soft-tissue cancers. All other causes of death, including cancers of the brain, lung, and lymphatic/hematopoietic system, were not consistent with a causal relationship.⁷

The VCHC appreciates your efforts to ensure that the descriptive language in the RoCs reflects the current scientific literature on the important subject of the carcinogenicity of vinyl chloride. Please contact the VCHC Manager, Elizabeth Festa Watson at 703-741-5629, if you would like additional information in support of these comments.

Sincerely yours,



Courtney M. Price
Vice President, CHEMSTAR

Enclosure

⁶ Mundt KA, Dell LD, Austin RP, Luippold RS, Noess R, Bigelow C. Historical cohort study of 10,109 men in the North American vinyl chloride industry, 1942-72; update of cancer mortality to 31 December 1995. *Occup Environ Med* 2000; 57:774-81.

⁷ Boffetta P, Matisane MD, Mundt KA, Dell LD. Meta-analysis of studies of occupational exposure to vinyl chloride in relation to cancer mortality. *Scan J Work Environ Health* 2003; 29(3): 220-29.